The Association Between Intestinal Flora and Lung Cancer and the Regulatory Role of Dietary Fiber

Huizi Wu*

College of Food Science and Engineering, Tianjin University of Science and Technology, Tianjin, 300457, China

*Corresponding author: wuhz2021@mail.tust.edu.cn

Abstract. Lung cancer accounts for a large proportion of malignant tumor-related deaths. In recent years many studies have demonstrated that dysbiosis is associated with carcinoma of the lungs. Intestinal flora is one of the most complex and diverse microbial populations in the human body. The intestinal flora can maintain a dynamic balance under normal circumstances and has the functions of promoting metabolism and enhancing immunity. This mechanism is partly dependent on short-chain fatty acids (SCFA) produced by the gut microbiota. Dietary fiber provides nutrition for intestinal flora, regulates the diversity and richness of intestinal flora. It also occupies a dominate position in the prevention and treatment of certain diseases. When lung cancer-related microbiota is modulated by dietary fiber, they may have an influence on the lung cancer development. In this paper, the mechanism of intestinal flora and dietary fiber affecting the role of intestinal flora and dietary fiber in lung cancer, respectively, and the correlation between them were summarized.

Keywords: Lung Cancer; Intestinal Flora; Dietary Fiber; SCFA; Prebiotics.

1. Introduction

Pulmonary primary malignant tumor is more familiar malignant tumors threatening human life and health in the world. According to WHO, lung carcinoma is the malignant tumor with the highest age-standardized incidence and age-standardized mortality in the world. The microbes such as bacteria, fungi, and so on live in the human gut, which together constitute the intestinal microecology. Under normal physiological conditions, all bacteria maintain dynamic balance to promote metabolism and immune defense functions, which is a necessary factor to maintain human health[1]. Thanks to the advent of genetic research tools and the metagenomic revolution of the past few decades, scientists have been able to describe the microbiota clearer and how they act on different parts of the body, and in particular to learn more about the microbes which inhabit the human gut. They are imperative parts to host metabolism and have been found to be associated with a variety of diseases. Recent studies have implied that the mechanism of lung cancer is closely related to human intestinal flora (IF). Dietary fiber provides nutrition for IF, regulates the diversity and richness of IF, and also plays a significant contributor in the prevention and treatment of some diseases. Most IF colonize the far end of the digestive tract, and after most nutrients have been absorbed, they use dietary fiber and other food residues that the host cannot digest, through fermentation, biosynthesis of some important metabolic byproducts such as essential amino acids, vitamins and short-chain fatty acids (SCFAs). It can stimulate multiple biological signaling pathways in the host, regulate energy homeostasis, affect tissue development, inflammation and immune processes and states, and play an important role in host health. Unlike the host genome, the IF is bidirectional plasticity, readily ADAPTS to environmental and host-derived stimuli, and its composition and activity are influenced by the host's genes, nutrition and lifestyle, and co-exist and develop with the host[2]. Among environmental factors, diet is a key factor affecting the genes and IF constitution[3]. In this paper, the mechanism of IF and dietary fiber affecting the role of IF and dietary fiber in lung cancer, respectively, and the correlation between them were summarized.

2. The Relationship Between IF and Lung Cancer

The microbiota in gastrointestinal tract, also known as the IF, is one of the most complex and diverse microbial populations in the human body. It has a complex mutualistic symbiosis with its human host. IF has a diversity of essential functions in the human gut, such as converting non-digestible food components into absorbable metabolites, essential vitamin synthesis pathways, clearing toxic compounds, enhances immunity, maintaining intestinal stability and so on[1]. Most of these functions are closely related to human physiological functions. Importantly, the broad IF should also include other acting microbes in addition to bacteria, such as archaea, viruses, phages, and fungi.These microorganisms may exert host control indirectly by microorganisms by controlling the activity of gut bacteria, which function as important as the function of bacteria.

The generation and development of lung cancer and other tumors are mostly related to low autoimmune surveillance function, immune system disorders, and systemic immunity suppression. There is growing evidence that the microbiome also occupy a dominant position in carcinogenic mechanisms. Researches have indicated that the human lung and IF have some similarities at the phylum structure level, and that the gut and lung microbiota populations, including their metabolites, transfer to each other through the blood and lymphatic circulation, forming a complex bidirectional axis connection, the gut-lung axis. IF can maintain lung immune function through intestinal-lung axis[2], to reduce the probability of lung lesions and even malignant progression. However, when the IF is dysfunctional, the intestinal mucosal barrier and immune function are impaired. This situation leads to harmful micro-flora changing the pulmonary microbial composition via intestinal -lung axis, forming an inflammatory micro-environment and triggering DNA damage. At the same time, it induces cell damage, secretes harmful metabolites, promotes angiogenesis and affects tumor stem cells. All these may destroy the lung immune homeostasis, inhibit the immune surveillance function, and promote the generation and development of lung cancer[4].

3. Relationship Between IF and Health

3.1. Effects of IF on Metabolism and Chemotherapy Efficacy

Chemotherapy remains the treatment of choice for patients with advanced non-small cell lung cancer, and the use of chemotherapy drugs affects the bacterial community structure. The abundance of enterobacter, enterococcus, Lactobacillus and streptococcus bacteria in the IF increased in patients treated with pemetrexed combined with cisplatin[5]. After the application of cyclophosphamide, the abundance of lactobacillus and enterococcus in the IF of mice was decreased. Specific gram-positive bacteria (such as Lactobacillus Jonii, Lactobacillus muris, etc.) were promoted to migrate to secondary lymphoid organs and stimulate the production of T cells. Mice with tumors that lacked gram-positive bacteria showed resistance to cyclophosphamide[6]. However, some Gram-positive microbacteria, such as Parabacteroides dieldii and segmentofilamentous bacteria, were found by ZITVOGEL et al. to reduce the effectiveness of chemotherapy drugs[7]. The anticancer effects of cyclophosphamide were significantly enhanced in tumour-bearing mice with 13,144 Enterococcus IGR11 (whose phage contains a dominant TMP epitope)[8]. In Lewis lung cancer mouse model, compared with cisplatin combined with antibiotics, cisplatin combined with Lactobacillus treatment significantly reduced the tumor in mice and significantly improved the survival rate[9].Konishi et al. found that the tumor suppressive molecule chromic iron produced by Lactobacillus casei ATCC334 can induce the apoptosis of c-Jun amino-terminal kinase signaling pathway, and its tumor inhibitory effect is better than cisplatin and 5-fluorouracil[10]. Spermidine, the amino acid metabolite of IF[11], can induce tumor autophagy, improve anti-cancer immune monitoring, induce anti-cancer immune response, and inhibit tumor growth. IF related vitamin B6 can cooperate with cisplatin and other chemotherapy drugs to kill NSCLC cells, and jointly mediate the immune-dependent anti-tumor effect[12].

The composition of IF is affected by chemotherapy, and IF can also regulate the activity of chemotherapy drugs, produce special metabolic substances that affect the tumor microenvironment and affect the therapeutic effect. Some scholars have put forward the concept of "pharmacomicrobiology"[13]. Therefore, focusing on the potency of the microbiome in drug metabolism and cancer treatment efficacy is expected to improve treatment outcomes by manipulating host-chemotherapy-microbiome interactions.

3.2. Effects of IF on Inflammation

The inflammatory micro-environment occupy a dominant position in the occurrence, development and sensitivity of tumor therapy, and is a significant part of the micro-environment. Clinical and epidemiological research indicated the strong correlation between chronic infection, inflammation and cancer[14]. For example, cigarette smoke and other irritating gases also act as lung cancer promoters in the process of triggering chronic inflammation in the lungs, Like chronic obstructive pulmonary disease, which is a high risk factor for lung cancer. At the same time, lung cancer patients often develop local infections (such as viral infections, pneumonia, or tuberculosis) and inflammation[15].

At present, it is generally believed that cancer-related inflammatory cells (including innate immune cells and adaptive immune cells) and their production of a variety of cytokines, such as chemokines, reactive oxygen species, matrix metalloproteinases and interferons[16], together form the tumor inflammatory microenvironment, mediating the occurrence and metastasis of tumors, and affecting tumors the formation of multiple abilities plays an important role. For example, MMPs are involved in various stages of tumor progression, including proliferation, differentiation, angiogenesis, senescence, autophagy, apoptosis, immune escape, invasion, or metastasis [17].

At present, the tumor inflammatory microenvironment has been considered as a principle element affecting the treatment and prognosis of lung cancer patients.

3.3. Effects of IF on Immune Regulation

Recently, immunotherapy has made breakthroughs in the treatment of lung cancer and is gradually changing the standard therapy regimen as well as prognosis for patients who has advanced NSCLC. The relationship between epidemic treatment and IF is complex because immunotherapy is more targeted, the applicable population may have limitations. IF influences on the immune system extends far beyond the local intestine, and its impact on the immune system is also related to effects of immunotherapy for lung cancer. Studies have shown that advanced NSCLC patients with high IF diversity respond significantly better to nivolumab treatment than patients with low diversity. In terms of PFS, patients with high IF diversity had a median PFS of 209 days, while patients with low IF diversity had a median PFS of 52 days. This may be related to the increase of peripheral memory T cells and natural killer cells in patients who has high IF diversity[18].

The experiment found that Oral bifidobacterium improved the response of antibodies against PD-L1 in mouse models of cancer by inducing dendritic cell function and improving the accumulation of CD8+ T cells in the tumor microenvironment[19]. The positive effects of the "good microbiome"[20] have also been demonstrated in clinical studies where Clostridium butyricum therapy (CBT) is performed immune checkpoint blocking (ICB) before and after treatment. The patients PFS and OS can be significantly prolonged with advanced NSCLC. Patients who received CBT had a median PFS of 250 days, while patients with advanced NSCLC who did not receive CBT had a median PFS of 101 days and a median OS of 361 days (terminal NSCLC patients who received CBT did not have a median OS). And, even in terminal NSCLC patients who had been take antibiotics treatment, CBT treatment observably prolonged PFS and OS. At the same time, the findings of Tomita et al[20] indicate that there are some mechanisms between IF and lung cancer to a certain extent.

At present, the mechanism by which IF plays the role of lung immunomodulation has not been fully clarified, but it may involve the following two pathways. The first is the "lung-gut axis" theory[2], in which antigens present and transfer IF and their products to mesenteric lymph nodes,

where stimulate of T and B cells activation. Once them become active, these cells acquire homing properties by expressing certain chemokine receptors (such as CCR4 and CCR9) and can migrate back to the original place (intestinal mucosa) or distal sites, such as the airway[21], through lymph and blood circulation. There, they can work directly on the target or go on to stimulates patients' immune systems. What's more, IF products or live flora can also reach the lungs directly through the blood or lymphatic circulation to prime the immune system. Lying on the type of stimulation the tissue receives as well as the immune state it is in, the results can be varied and may produce potent anti-inflammatory or anti-tumor activity, or may further promote tissue damage, pathogen colonization, and tumor progression. The second is the "gut-bone marrow" regulatory mechanism[22]. The metabolites of IF are the sources of microbe associated molecular patterns (MAMPs) and PAMP. The MAMP or PAMP activates PRRs by binding to immune cells just like monocytes, macrophages, and natural killer cells.

At the same time, these microbe-derived antigens arrive to the bone marrow through the blood circulation and affect the differentiation and function of myeloid immune cells, inducing the production of cells with long-term "memory" properties. Zitvogel et al. suggested that these antigens from IF were similar to tumor antigens[23]. The activity of immune cells was stimulated by antigen simulation or cross-reaction, and the corresponding T cell bank was formed. Therefore, it improves the reactivity and anti-tumor ability of the immune system when recognizing cancer cells, that is, enhances the immune surveillance ability. In addition, Dang et al. found that SCFAs in IF products can play an immunomodulatory function by promoting the production of bone marrow hematopoietic precursors[24].

4. The Relationship Between Dietary Fiber and Health

Dietary fiber (DF) was first proposed in the 1950s. With the further study of dietary fiber, its definition has been continuously improved. The WHO and FAO define dietary fiber as: not digestible and absorbed in the small intestine, degree of aggregation not less than 10 carbohydrate polymers[25]. According to their ability to dissolve in hot or warm water, they are also including soluble dietary fibers soluble dietary fiber (SDF) and insoluble dietary fiber (IDF). Dietary fiber is a nutrient that cannot be replaced by other substances to maintain human health. It is called the "seventh nutrient" of the human body after the six nutrients of carbohydrates, fat, egg albumin, vitamin, water and minerals.

Dietary fiber can promote health through a diversity of mechanisms including not only direct and but also indirect influence. Direct effects include the biochemical and structural properties of dietary fiber (water retention, expansibility, and binding fat, etc.). For example, due to slow digestion, hard-to-digest dietary fiber cannot be hydrolyzed by the body's digestive enzymes directly to the large intestine, thus reducing postprandial blood sugar levels. Soluble dietary fiber is a sticky substance that forms a gel, delaying stomach emptying time and preventing cholesterol accumulation. Insoluble dietary fiber can promote intestinal peristalsis and make excretion easier. The indirect effect mainly depends on the regulation of intestinal microorganisms, the production of SCFAs, the reduction of intestinal pH, the improvement of mineral bioavailability, and the effect on host health.

4.1. Regulates Host Energy Metabolism

SCFAs are the products of the fermentation of dietary fiber in the large intestine which can make activation of GPR109a, GPR41, GPR43, etc., enhance the differentiation of intestinal endocrine cells, promote hormone production, and thus reduce appetite. For example, intestinal endocrine cells can secrete hormones GLP-1 and PYY, and gastric acid and leptin. GLP-1 can promote insulin production, improve insulin sensitivity, and increase satiety. Other hormones, including PYY, OXM, and leptin, suppress appetite, increase satiety, and regulate energy metabolism.

4.2. Improve Inflammation and Maintain Intestinal Barrier Homeostasis

SCFAs produced by dietary fiber can decrease intestinal permeability, prevent metabolic disorders, advance intestinal barrier function, and have lower LPS translocation. SCFAs has also been reported to have anti-inflammatory effects as a histone deacetylase inhibitor. SCFAs regulate the size of colon Treg and function induce Foxp3+IL-10-Tregs[26]. SCFAs also regulates GPR109a and GPR43, promote intestinal epithelial cells to secrete anti-inflammatory factors IL-10 and IL-18[27].

4.3. Regulates Glycolipid Metabolism

SCFAs produced by the fermentation of dietary fiber can inhibit liver glycoldecomposition, reduce blood glucose production and improve insulin sensitivity. Dietary fiber also decreased the expression of fat forming genes and increased the expression of lipolysis genes. SCFAs can reduce cholesterol production and fat formation dependent on sterol regulatory element binding proteins, or alter PPARα-driven fatty acid oxidation[28]. SCFAs also regulates hepatic glycoconeogenesis and lipid biosynthesis by regulating PPARγ and AMPK pathways. SCFAs can enhance insulin sensitivity and glucose tolerance by regulating intestinal glycogenogenesis (IGN) in intestinal epithelial cells[29].

4.4. Improve Intestinal Immunity

Dietary fiber can increase the abundance and variety of IF, increase the number of fiber degrading bacteria, and reduce the number of mucus-degrading bacteria. SCFAs produced by dietary fiber can promote the production of Muc2 and the thickness of mucous layer. The first line of defense against pathogens is the mucus layer, which is intestinal cell production[30]. Dietary fiber can affect the immune response because a large number of immune cells colonize the intestinal lamina propria, including neutrophils, dendritic cells and so on.

5. Effects of Dietary Fiber on IF and Lung Cancer

People cannot digest and decompose dietary fiber, and dietary fiber is decomposed into SCFAs by IF fermentation. Studies have shown that SCFAs are of great significance to various organs such as the intestine and lungs. A high dietary fiber diet can alter the lung immune environment by altering the gut microbiome with the lung microbiome. In the current study, lung cancer risk was inversely relating to dietary fiber intake.

A lot of studies have indicated that obesity is closely related to the pathogenesis of many cancers. Increasing the part of dietary fiber in the daily diet can decrease the intake of carbohydrates and fats. At the same time, weight control can indirectly prevent the development of cancer. The growth of cancer cells is accompanied by a large number of rapid mitosis processes, and a large number of studies have confirmed that high insulin can promote mitosis[32], so high insulin levels can promote the development of cancer. Dietary fiber intake can reduce the intake of carbohydrates, thereby reducing insulin levels, so it can indirectly inhibit the development of cancer. However, some studies have also proved that certain insulin analogues have the function of inhibiting the development of cancer[33]. This mode of action of dietary fiber on cancer needs further study.

Dietary fiber can also affect the body's immune system, resulting in anti-cancer effects. It was found that dextranan microparticles can activate the dectin-1 receptor of dendritic cells and increase the expression of glycated hemoglobin tumor necrosis factor receptor (GITRL). It also proved that the proliferation of T cells by GITRL pathway can delay tumor progression[34]. Another in vitro study also found that β-glucan can be used on some immune receptors just like Dectin-1, CR3, and TLR-2/6, and then induce the action of immune cells, including macrophages, neutrophils, monocytes, natural killer cells, and dendritic cells[35].

In order to study the effect of oat glucan on lung tumors, rats were given glucan solution for 10 days, and the melanoma cells were inoculated intravenously. After 14 days, the rats were killed. Morbidity of lung cancer was inferior in the glucan group, while the growth of macrophages was higher. Oat glucan can effectively prevent the growth and metastasis of lung cancer cells, which may

activate the anti-tumor effects of macrophages and killer cells (NK cells)[36]. Animal experiments have proved that β-glucan has an activation influence on the immune system and a killing effect on cancer cells. The mushroom polysaccharides extracted from ganoderma lucidum can enhance the cytotoxicity mediated by NK cells, thus inhibiting the growth of Lewis lung adenocarcinoma cells. Binding β-glucan to radiotherapy in mice with lung cancer helped control tumor growth and metastasis, and had a protective effect on normal tissue in mice and reduced hair loss caused by radiotherapy[37].

Yogurt is a nutrient-rich food that often contains specific probiotics and prebiotics that can also enhance the community activity of IF. In addition, probiotics, an immunomodulator, mediate the secretion and proliferation of cytokines to differentiate immune cells. Both vivo and in vitro studies have implicated that lung metastasis is inhibited by certain probiotics, improved the activity of natural killer cells, and have anti-tumor and anti-tumor effects. Prebiotics are also a type of dietary fiber, and prebiotics and probiotics have a synergistic impress on host health. Experiments have shown that probiotics produced by the fermentation of prebiotics are beneficial to human health in the colonization of the intestinal tract by bifidobacterium and lactobacillus, and improve the ecological environment of intestinal microorganisms. Increasing the intake of prebiotics and probiotics has the potential to prevent lung cancer[3].

6. Conclusion

The importance of intestinal flora to local gut and overall host health is being recognized again. In recent years, the presence of intestinal flora and its role in lung cancer have also received much attention. Intestinal flora is constantly reregulated with the stage of lung cancer development, the intervention of chemotherapy drugs and other therapeutic measures, and can also play a remote role in lung cancer through metabolism, inflammation and immune response. The results show that dietary fiber is as important as other essential nutrients in maintaining intestinal microecology and improving body health. Long-term intake of adequate dietary fiber can maintain healthy intestinal environment and improve the biodiversity of intestinal microbes, thereby preventing chronic diseases or improving their symptoms. Therefore, with the continuous deepening of research, it will be possible to use intestinal flora to intervene in the treatment of lung cancer. Meanwhile it is expected to achieve the purpose of improving the survival period and quality of life of lung cancer patients. At present, it is still unclear the exact mechanism by which intestinal flora affects the therapy of lung cancer, and which more specific strains affect the efficacy of lung cancer through which regulatory mechanisms, nor is it clear whether the benefits of intestinal flora can be maximized by strictly controlling the number of intestinal florae. With the deepening of research, it is possible to use intestinal flora to intervene in the treatment of lung cancer, which is expected to enhance the survival period and living quality of cancer patients.

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